

The University of Chicago

URACIL DERIVATIVES

A DISSERTATION SUBMITTED TO THE
FACULTY OF THE DIVISION OF THE
PHYSICAL SCIENCES IN CANDIDACY FOR
THE DEGREE OF DOCTOR OF PHILOSOPHY

DEPARTMENT OF CHEMISTRY

1937

By

WENDELL PHILLIPS METZNER

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I. INTRODUCTION

The relief of pain and the alleviation of sleeplessness represent two distinct pharmacological activities of drugs. The two functions are found combined in a single substance only in opium and its two most important active principles, morphine and codeine, the effects being dependent to some extent on the dosage used. It is this combination of analgesic and hypnotic actions that makes morphine such a valuable drug, and, properly used, still indispensable to mankind. However, it is well known that the use of morphine all too readily leads to the formation of a deplorable habit, which wrecks the lives of its unfortunate victims. These facts have served as an incentive for the preparation of synthetic analgesics and hypnotics. It has not been found possible to combine the two activities in a single artificial product. Medicine is quite content to achieve its purpose by the simultaneous use, when necessary, of two drugs: one an analgesic and the other a hypnotic, each in the dosage the art of the physician considers desirable.

The result is that morphine is used today only in those cases in which intense suffering is not relieved by the activity of the synthetics. For the reason that the sedatives prepared by man have failed in such acute cases, and that morphine with its dangerous possibilities is still the ultimate recourse of medicine, further effort toward the discovery of more effective drugs in this field is indicated. Progress is being rapidly made in the matter of hypnotics, but advances in the development of more powerful analgesics have been almost negligible. Practically

nothing has been done toward combining the two functions in a single synthetic. Such a union might very well be the essential characteristic necessary for arriving at analgesic powers of the order shown by morphine.

The present investigation was undertaken as an effort toward combining analgesic and hypnotic powers in a single synthetic at the suggestion of Professor Stieglitz and carried out under his direction.

It is well known that 5,5-di-alkyl and 5,5-alkyl-aryl derivatives of barbituric acid, a ureide of malonic acid, have been found to be the best hypnotics thus far synthesized. Since Emil Fischer¹ prepared diethyl barbituric acid, $(C_2H_5)_2C.CONHCONHCO$, known as veronal (or, officially, as barbital) wide deviations in structure have led to synthetic hypnotics of varied pharmacological properties, which find application in medicine. Such structural modifications usually are accomplished by varying the character of the alkyl groups and by alkylation of the urea group.

On the other hand, of the analgesics, aside from the very mild action of acetylsalicylic acid (aspirin), probably the most useful have been antipyrine, $CH_3C:CHCONC_6H_5.NCH_3$, a pyrazolone obtained from acetoacetic ester and phenylhydrazine with subsequent methylation, and the dimethylamino derivative of antipyrine, aminopyrine, $CH_3C:CN(CH_3)_2.CONC_6H_5.NCH_3$.

Synthetic work on the preparation of ureides of acetoacetic ester with possible hypnotic powers has been in progress in this laboratory for several years. It was thought desirable to include in this series some dialkylamino uracils of the general type $HNCONH.C(CH_3):C(NR_2)CO$ and their N-alkyl and N-aryl derivatives. Such compounds, it was thought, might be found to combine

¹Ann., 335, 334 (1904).

in a measure the analgesic properties of an aminopyrine with the hypnotic qualities of the barbitals, with an enhancement of the analgesic character.

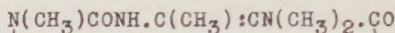
The preparation of dialkylaminouracils started from 5-bromouracils, such as $\text{HNCONH.C(CH}_3\text{):CBr.CO}$. This path suggested a study of the reactions of 4-methyl-5-bromo-5-ethyluracil, $\text{HNCON:C(CH}_3\text{).CBr(C}_2\text{H}_5\text{)CO}$, particularly as a possible gateway to the preparation of 4-methyl-5,5-diethyluracil, $\text{HNCON:C(CH}_3\text{).C(C}_2\text{H}_5\text{)}_2\text{CO}$. This compound has been an objective of a series of investigations in this laboratory and thus far has eluded all efforts to prepare it--probably on account of stereochemical interferences. We were no more successful than previous investigators. The work done in this direction will be included in this report, particularly since it led to the interesting observation of a migration of bromine previously observed in the case of α -bromoacetoacetic ester, but apparently not in the case of uracils.

II. DISCUSSION OF RESULTS

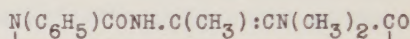
No particular difficulty was met in the preparation of the following 5-dimethylamino uracils:

1. 4-methyl-5-dimethylamino uracil, $\text{NHCONH.C(CH}_3\text{):CN(CH}_3\text{)}_2\text{.CO}$

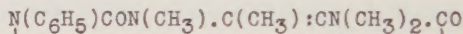
2. 1-4-dimethyl-5-dimethylamino uracil,



3. 1-phenyl-4-methyl-5-dimethylamino uracil,

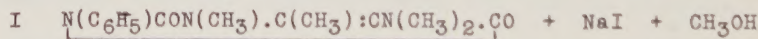
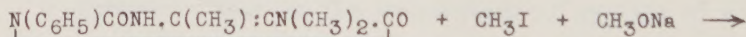


4. 1-phenyl-3-4-dimethyl-5-dimethylamino uracil,

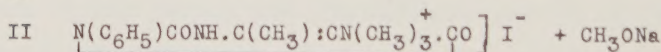


The general procedure followed in the cases of the first and third uracils involved the preparation of the indicated uracil, its 5-bromo derivative, and treatment of the latter with aqueous dimethylamine in a sealed tube. The second compound listed above was prepared from the first by methylation with methyl iodide.

The fourth uracil mentioned, the exact ureide analog of aminopyrine, was obtained by treating the third with methyl iodide. When 1-phenyl-4-methyl-5-dimethylamino uracil is treated with an equal molecular quantity of methyl iodide, two possible products might be formed:



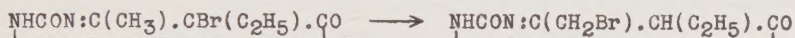
or



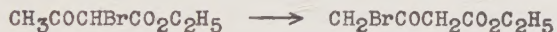
The reaction as conducted by the author formed entirely the prod-

uct given in equation I as shown by analytical data.¹

Of greater theoretical interest were the observations made in the study of 4-methyl-5-bromo-5-ethyl uracil, including the effort to replace the bromine atom by a second ethyl group. From the evidence gathered,² it appears that this compound is one that rearranges on standing. The freshly prepared bromo-derivative of 4-methyl-5-ethyl uracil has the bromine on the desired carbon -5 atom, but, after standing for a period of six months, the bromine has migrated to the methyl group on position 4:



The same type of rearrangement has been shown to occur in brominated acetoacetic ethyl ester.³ On standing several weeks at ordinary temperatures, α -bromo acetoacetic ethyl ester is transformed into the corresponding γ -bromo compound:



Since acetoacetic ethyl ester is used as one of the starting materials and the carbon chain is kept intact in the preparation of 4-methyl-5-ethyl-5-bromo uracil, it is not unreasonable to expect the uracil to retain properties characteristic of the α - and γ -carbon atoms in the original ester.

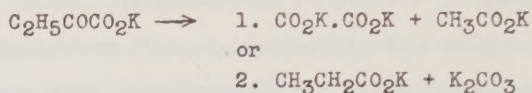
The above conclusions regarding the position of the bromine atom were based on oxidation of fresh and old bromo-compounds with alkaline potassium permanganate and identification of the resulting fragments. 4-Methyl-5-ethyl-5-bromo uracil should give on oxidation with alkaline permanganate principally acetylurea, potassium bromide and, possibly, potassium oxalate, potassium

¹See Experimental Part, p. 12.

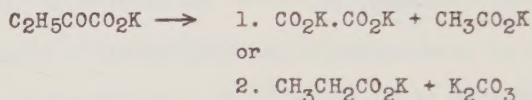
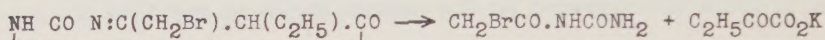
²See Experimental Part, p. 13.

³A. Hantzsch, Ber., 27, 356, 3186 (1894).

propionate or potassium acetate:



After the bromine atom has migrated to the 4-methyl group, oxidation would form mostly bromoacetylurea and, possibly, potassium oxalate, potassium propionate or potassium acetate:



When a sample of brominated 4-methyl-5-ethyl uracil that was six months old was submitted to oxidation with alkaline potassium permanganate, two products of the reaction were identified (no search was made for acetic or propionic acids). Oxalate ion was shown to be present and a second substance which had physical constants and analytical data comparable to those of Baeyer's¹ bromoacetylurea was separated from the reaction mixture. This material obtained by us softened at 161° and completely melted into a brown liquid at 175°; bromoacetylurea had corresponding changes at 160° and 176-77°. ² Both substances are easily soluble in hot ethyl alcohol and hot water, but difficultly soluble in the cold solvents. A mixture of equal quantities of the oxidation product and synthetic bromoacetylurea softened at 161° and melted to a brown liquid at 173-174°. Quantitative analytical

¹Ann., 130, 156 (1864).

²Baeyer did not record a melting point for bromoacetylurea. The present author determined the melting point for a product prepared according to Baeyer's procedure in Ann., 130, 156 (1864).

data showed the oxidation product to have 47.80% bromine and 10.38% nitrogen as compared with 44.20% bromine and 15.46% nitrogen for bromoacetylurea.

Freshly brominated 4-methyl-5-ethyl uracil gave a quite different result when oxidized in exactly the same way as the material that was six months old. Oxalate was shown to be present as before. No crystalline solid could be obtained from the organic gum that was formed by the oxidation. This gum contained nitrogen, but no bromine, as shown by a qualitative sodium fusion test; moreover, a quantitative determination by the Parr bomb method indicated complete absence of halogen. A qualitative halogen test showed bromine to be present as bromide ion in the inorganic fraction of the oxidation products. Thus one must conclude that any substance isolated from the gum must be halogen-free. A uracil derivative having bromine in position 5 would have the halogen removed by oxidation¹ and give results analogous to those obtained by the author.

These results show that brominated 4-methyl-5-ethyl uracil does undergo a transformation when kept for some time at room temperature. Further work is being conducted in this laboratory to obtain confirmatory data.

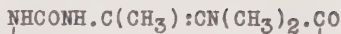
The 4-methyl-5-ethyl-5-bromo uracil was used as a stepping stone for obtaining 5,5-dialkyl uracils. The substitution of an alkyl group for bromine was attempted by treatment of the uracil with a Grignard reagent. Although the uracil was rather insoluble in all of the solvents ordinarily used, it was decided to run a reaction of ethyl magnesium bromide with the bromo-compound suspended in dry ethyl ether. A reaction must have

¹G. Offe, Ann., 353, 267 (1907).

occurred since much gas was liberated; however, only original uracil and an organic substance that melted above 330° were separated from the mixture. This latter was not identified.

III. EXPERIMENTAL PART

1. 4-Methyl-5-dimethylamino uracil,



Pulverized 4-methyl-5-bromo uracil (10 g.) was placed with 10 g. (50% excess) of 33% aqueous dimethylamine in a bomb tube. The reaction was run at 140-150° for six hours. The brown contents of the bomb were evaporated to a thick paste on the steam bath and taken up in about 400 cc. of boiling 50% ethyl alcohol. The solution was treated with animal black, filtered hot, and the filtrate chilled to effect precipitation of the uracil. A second crop was obtained by concentration of the filtrate. The precipitate was purified by recrystallization from 50% ethyl alcohol. Large colorless plates were formed that decomposed above 291°. The yield was 5.3 g. of the dimethylamino-derivative from 10 g. of the bromo-compound, or 65% of theory. The product was soluble in hot ethyl alcohol, sparingly soluble in cold alcohol and hot water, and insoluble in cold water. Analyses¹ for carbon, hydrogen, and nitrogen resulted in these data:

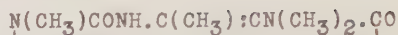
Calculated for $\text{C}_7\text{H}_{11}\text{O}_2\text{N}_3$: C, 49.67% ; H, 6.56% ; N, 24.85%

Found: " 49.88 ; " 6.93 ; " 24.88

" 49.69 ; " 6.89 ; " 24.60

¹Pragl's micro methods were used in all the analyses given in this report.

2. 1-4-Dimethyl-5-dimethylamino uracil,



Sodium (0.9 g., 20% excess, cut under ligroin) was dissolved in 60 cc. of absolute methyl alcohol and 5.5 g. of 4-methyl-5-dimethylamino uracil added to the solution. The mixture was heated 20 minutes to insure complete solution of the uracil. A slight excess of methyl iodide (5.7 g.) was slowly added and the whole refluxed 12-15 hours. The alcohol was removed by evaporation on a steam bath and finally in a vacuum desiccator. The best method found for getting the resulting syrup to crystallize was to dissolve this oily mass in small amounts of water contained in shallow dishes. Sodium iodide formed in the reaction was dissolved and crystallization of the 1-4-dimethyl-5-dimethylamino uracil was effected. The crystalline product was readily recrystallized from small amounts of hot ethyl alcohol. The colorless needles decomposed 270-275°. A yield of 2.9 g. of the methylated derivative was obtained, which represents a yield of 50% of theory. The compound was soluble in hot water, hot ethyl alcohol, and sparingly soluble in hot ether. It was insoluble in cold water, alcohol and ether, and both hot and cold ligroin and xylene. Nitrogen determinations gave:

Calculated for $\text{C}_8\text{H}_{13}\text{O}_2\text{N}_3$: N, 22.93%

Found: " 23.10

" 23.13

3. 1-Phenyl-4-methyl-5-dimethylamino uracil,



1-Phenyl-4-methyl-5-bromo uracil (6 g.) was placed in a bomb tube with twice the theoretical quantity of 33% aqueous dimethylamine (6 g.) and the reaction run at 140-150° for six

hours. The contents of the bomb were evaporated to a paste, which was taken up in hot 50% ethyl alcohol. The solution was treated with charcoal to remove discoloration. The charcoal was removed by filtration and the filtrate chilled. The precipitate formed was recrystallized from more 50% alcohol. The pure needles melted sharply at 241° . The yield was 2.6 g. from 6 g. starting material, or 50% of theory. The product was soluble in cold alcohol and sparingly soluble in hot water, but insoluble in ether, ligroin, and cold water. 3 Nitrogen analyses gave the results:

Calculated for $C_{13}H_{15}O_2N_3$: N, 17.11%

Found: " 17.07

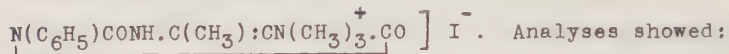
" 17.06

4. 1-Phenyl-3-4-dimethyl-5-dimethylamino uracil,



Sodium (0.46 g., 25% excess) was dissolved in 40 cc. of absolute methyl alcohol contained in a small flask fitted with a reflux condenser. 1-Phenyl-4-methyl-5-dimethylamino uracil (3.7 g.) was added to the solution and the mixture heated for twenty minutes on the steam bath to insure complete solution of the uracil. Methyl iodide (2.9 g., 25% excess) was slowly added to the solution and the whole refluxed for 15-20 hours. The alcohol was then removed by evaporation and the residual oil poured into a small amount (50 cc.) of cold water. The oil soon solidified and the product was collected on a filter. After the crude preparation was recrystallized from 50% alcohol, the fine needles melted with decomposition at 240° . The yield was 52% of theory. The product is soluble in hot water and hot alcohol, but insoluble in ligroin, ether and cold water. A negative Beilstein halogen test and a quantitative nitrogen determination

showed that the compound was not a salt having this formula:



Calculated for $\text{C}_{14}\text{H}_{17}\text{O}_2\text{N}_3$: N, 16.22%

Found: " 16.34

" 16.39

5. Bromination of 4-methyl-5-ethyl uracil.

Finely pulverized 4-methyl-5-ethyl uracil (6.5 g.) was suspended in 100 cc. of carbon disulfide in a glass-stoppered bottle. Bromine (8.1 g., 20% excess) was added with shaking and cooling. Hydrogen bromide was formed immediately as indicated by fuming of the gas in the bottle. When the rather violent reaction ceased, the bottle was sealed and placed on a shaker to insure complete reaction of uracil and bromine. The bottle was arranged so that all the solid was kept in contact with the bromine-carbon disulfide mixture. Small amounts of unreacted uracil were hard to remove and greatly lowered the melting point of the bromo-uracil.

After the mixture was shaken for 18-20 hours, the red solid was collected on a filter and washed several times with fresh carbon disulfide. The solid was then spread out on clay plates at room temperature to facilitate removal of carbon disulfide, hydrogen bromide and bromine.¹ The slightly colored bromo-derivative was recrystallized from hot ethyl alcohol, in which it is quite soluble. Colorless needles were formed, which melted with effervescence about 248°. A yield of 8.0 g. of brominated 4-methyl-5-ethyl uracil was obtained from the 6.5 g. of starting product, or 82% of theory. Solubility of the com-

¹It was thought that heating such a bromo-compound would probably decompose it by splitting off ethylbromide.

pound in various solvents was determined. It was found to be insoluble in these solvents (both hot and cold): benzene, ligroin, diethyl ether, dibutyl ether and anisol. It was soluble in hot ethyl alcohol, hot water, pyridine, glacial acetic acid and carbitol. Analysis of the compound gave the following results:

Calculated for $C_7H_9O_2N_2Br$: N, 12.02% ; Br, 34.33%

Found: " 11.97 ; " 34.36

" 12.19 ; " 34.30

6. Proof of structure of brominated 4-methyl-5-ethyl uracil.

As was mentioned before,¹ it appears that this compound undergoes a rearrangement on standing at room temperature. When oxidized with alkaline potassium permanganate, freshly prepared material gave results entirely different from some which was six months old.

The oxidation was conducted in much the same manner as Offe² used in his proof of structure of 4-methyl-5-bromo uracil. Brominated 4-methyl-5-ethyl uracil (3.21 g.) was dissolved in 75 cc. of warm (40°) water by adding about 20 cc. of 5% potassium hydroxide solution. This solution, when cooled, was placed in a three-necked flask fitted with a mechanical stir having a mercury seal and a dropping funnel. A solution of 2.9 g. potassium permanganate (equivalent to two mols of oxygen) in 70 cc. of water was then slowly added through the dropping funnel with good stirring. Any gases escaping from the reaction were conducted through a trap containing standard acid. The reaction was run varying

¹See page 5.

²Ann., 353, 272 (1907).

lengths of time, but twenty hours assured complete oxidation. After this period of reaction, the filtrate obtained from the removal of manganese dioxide was almost colorless. When a shorter period of time was allowed for the reaction, the filtrate had a dark brown color.

When the oxidation was completed, the gases contained in the reaction vessel were forced into the standard acid with a stream of air. It was thought that some ammonia might be formed and liberated from the basic solution, but titrations of the standard acid before and after reaction indicated no ammonia formation. Manganese dioxide was filtered from the solution and the filtrate carefully neutralized with dilute hydrochloric acid.

The presence of much oxalate in the neutralized filtrate was ascertained by precipitating a calcium salt that was insoluble in acetic acid, but soluble in dilute hydrochloric acid. The calcium oxalate was washed with acetic acid, ignited, and weighed as calcium oxide. From the oxidation of 3.21 g. of starting material, there was obtained 0.153 g. calcium oxide, which represents a yield of 0.242 g. of oxalate ion. The solution remaining from precipitation of oxalate ion was concentrated at 40° with a stream of air and neutrality maintained during the evaporation. No test was made for propionic or acetic acids. Since the results from the oxidation of fresh and old brominated 4-methyl-5-ethyl uracil were quite different, the rest of the procedure will be divided into two parts: A, results obtained from oxidation of brominated 4-methyl-5-ethyl uracil six months old; and B, determinations made on material formed by oxidation of the freshly prepared bromo-compound.

A. When the neutralized solution of oxidation products obtained from six months old brominated 4-methyl-5-uracil was

concentrated to half its volume, a precipitate formed. More of this substance deposited while the solution was evaporated to a volume of 10 cc. After chilling the small volume of oxidation material, the precipitate was collected on a filter and washed with a small amount of water. The organic fraction of the precipitate was separated by extractions with small amounts of hot absolute ethyl alcohol. When chilled, the alcohol solution deposited a white solid. The yield was 0.3 g. from 3.21 g. of the starting uracil. It was recrystallized twice from hot ethyl alcohol. This substance had physical constants and analytical data comparable to those of Baeyer's¹ bromoacetylurea:

	<u>Oxidation Product</u>	<u>Bromoacetylurea</u>
Melting point	Softened 161°; melted to brown liquid 175°	Softened 160°; melted to brown liquid 176-77°
Solubility	Soluble hot alcohol	Soluble hot alcohol
	Soluble hot water	Soluble hot water
	Insoluble cold water and cold alcohol	Insoluble cold water and cold alcohol
Br	47.80%	44.20%
N	10.29% and 10.47%	15.46%

A mixture of equal quantities of the oxidation material and bromoacetylurea softened at 161° and melted to brown liquid at 173-74°, which decomposition point indicates that the two are the same substance.

B. No precipitate was deposited from the neutralized solution of oxidation material obtained from freshly brominated 4-methyl-5-ethyl uracil until the volume had been concentrated to 10-15 cc. This solid was collected on a filter and extracted as before with several small portions of hot absolute alcohol,

¹Ann., 130, 156 (1864).

but when chilled, the solution gave no precipitate; moreover, when the alcohol was completely removed by evaporation, only inorganic material remained. The solution of oxidation products was then evaporated to a gummy mass on the steam bath at 40° , and finally dried in a vacuum desiccator over sulfuric acid. The resulting gum and crystals were extracted four times with 10 cc. portions of hot absolute alcohol. The alcohol-insoluble residue was entirely inorganic as it did not char when heated in a flame, and gave a heavy precipitate when an aqueous solution of it was acidified and treated with silver nitrate solution. A qualitative test for bromide ion was positive: when a water solution of the inorganic fraction was shaken with chlorine water, a reddish coloration was imparted to a layer of carbon tetrachloride.

The yellow alcoholic extract was evaporated to a gum on the steam bath. When dried two days in a vacuum desiccator, this gum became entirely dry and could be powdered. However, it was so hygroscopic that when taken from the desiccator, it immediately became sticky and gummy. The yellow mass was extracted with all the organic solvents that could be obtained with the hope of separating a crystalline solid, but to no avail. The gum was soluble only in water and hot alcohol. When the hot alcohol solution was chilled, a copious precipitate formed, but after collection on a filter, this deposit was gummy as before. By a qualitative sodium fusion test the gum was found to contain nitrogen, but no halogen. Moreover, a quantitative determination by the Parr bomb method indicated a complete absence of halogen.

7. Treatment of brominated 4-methyl-5-ethyl uracil with a Grignard reagent.

The brominated uracil was treated with $2\frac{1}{2}$ times the theory of ethyl magnesium bromide because one mol of a Grignard

reagent replaces the hydrogen atom in position 1 of uracils. Dry magnesium turnings (1.1 g.) were covered with absolute ether in a three-necked flask fitted with a reflux condenser, a stirrer, and a dropping funnel. An ether solution of 4.7 g. of dry ethyl bromide was added dropwise from the dropping funnel with good stirring. After all of the ethyl bromide was added to the mixture, the whole was heated on a steam bath for thirty minutes to complete the formation of ethyl magnesium bromide. The dropping funnel was then replaced by a container used to add solid material in small portions to a reaction run in a closed vessel. Brominated 4-methyl-5-ethyl uracil (4.0 g.), suspended in absolute ether, was slowly added to the Grignard reagent from this special container. There was a vigorous evolution of gas which indicated a reaction must have taken place. The contents of the flask were refluxed for two hours and then hydrolyzed with 25% sulfuric acid. The ether layer was separated and, when evaporated to dryness, left no residue. The acid layer deposited some of the original uracil and a solid which charred in a flame, but did not melt at 335°.

This method of preparing 5-5 dialkyl uracil derivatives was postponed until the position of the bromine in brominated 4-methyl-5-ethyl uracil was definitely ascertained.

8. Treatment of brominated 4-methyl-5-ethyl uracil with aqueous dimethylamine.

Finely pulverized brominated 4-methyl-5-ethyl uracil (2.0 g.) that was two months old was suspended in 2.4 g. (twice the theory) of 33% aqueous dimethylamine in a closed test tube. The reaction was carried out at room temperature. The uracil gradually dissolved, and, by the fourth day, all the solid was in solution. The liquid was evaporated on the steam bath with a

stream of air until a solid separated. After chilling the solution, the precipitate formed was collected on a filter and recrystallized twice from hot water. White needles were formed that melted at 162° . The yield was .8 g. from 2 g. starting material, or 50% of theory. An analysis gave this result:

Calculated for $C_9H_{15}O_2N_3$: N, 21.32%

Found: " 21.52

" 21.65

9. 1-Phenyl-4-methyl uracil, $N(C_6H_5)CONH.C(CH_3):CHCO$

Behrend, Meyer, and Buchholz¹ prepared this uracil by condensing β -aminocrotonic ester with phenylisocyanate in the cold. The present author obtained approximately the same yields by running the condensation at room temperature for three days instead of eight days at a lower temperature. A by-product is always obtained regardless of the conditions used.

A. Preparation of β -aminocrotonic ethyl ester.²

Acetoacetic ethyl ester (65 g.) was dissolved in 95% ethyl alcohol (100 cc.) and gaseous ammonia passed through the resulting solution. Good stirring was maintained to facilitate a complete reaction during the treatment with ammonia (30 hours). The alcohol was removed under reduced pressure and the remaining oil chilled in ice. All of it solidified and the product was recrystallized from a very small amount of warm ethyl alcohol. It was dried in a vacuum desiccator over sulfuric acid. The β -aminocrotonic ester melted at room temperature. The yield was 42 g., or 65% of theory.

¹Ann., 314, 222 (1901).

²Lidov, Unpublished work.

B. Condensation of β -aminocrotonic ester with phenylisocyanate.

β -aminocrotonic ethyl ester (7.4 g.) was dissolved in absolute ether (40 cc.) in an Erlenmeyer flask and phenylisocyanate (6 g.) added. The flask was stoppered and the reagents allowed to react three days. Long needles of the by-product were noticed after three or four hours. The solid in the flask was collected on a plain filter and extracted once with fresh ether, and the remaining solid rejected. The ether solution was evaporated to dryness with a stream of air. The solid obtained from the ether solution (7 g.) was crude phenyluraminocrotonic ethyl ester (the unclosed ring) in yields of 56% of theory. This material melts 65-80°, but is pure enough for conversion into the uracil. Phenyluraminocrotonic ethyl ester (7 g.) was dissolved in a hot (85-90°) 10% potassium hydroxide solution (90 cc.) with good stirring. A small amount (.8 g.) of insoluble material was removed by filtration. The cooled filtrate was carefully neutralized with concentrated hydrochloric acid. The precipitate, 1-phenyl-4-methyl uracil, was collected on a filter and washed with a little water. The material melted at 244-246° with decomposition. The yield was 3.9 g. of the uracil from 6 g. phenylisocyanate used, or 39% of theory.

C. 1-Phenyl-4-methyl-5-bromo uracil,



1-Phenyl-4-methyl uracil (13.7 g.) was placed in a glass-stoppered bottle with 200 cc. of carbon disulfide and 15 g. (25% excess) of bromine. After the first rather violent reaction, the bottle was stoppered and shaken for twenty-four hours to insure complete reaction. The bottle was arranged in the shaker so that the bromine-carbon disulfide mixture constantly bathed the solid.

The red solid was collected on a filter, washed with fresh carbon disulfide, and spread out on a plate to dry. Last traces of the reddish-yellow color were removed by warming and stirring the material on a steam bath. The melting point, 242-243° + decomposition, agreed with that given for 1-phenyl-4-methyl-5-bromouracil prepared by a different method.¹ A yield of 18 g. of the bromo-derivative was obtained from the 13.7 g. of starting material, or 96% of theory.

10. 4-Methyl-5-ethyl uracil, $\text{NHCON:C}(\text{CH}_3).\text{CH}(\text{C}_2\text{H}_5).\text{CO}$

A. Condensation of α -ethyl acetoacetic ester with O-ethyl urea.

Lowe's method as reported by Terre² was used in condensing O-ethyl urea with α -ethyl acetoacetic ethyl ester to form 2-ethoxy-4-methyl-5-ethyl-6-oxypyrimidine. The yields ranged from 25% to 28% of theory.

α -ethyl acetoacetic ester was prepared according to Lowe's³ procedure. One mol (23 g.) of sodium was dissolved in 300-400 cc. (7-8 mols) of absolute ethyl alcohol in a flask fitted with a reflux, and one mol (130 g.) of redistilled acetoacetic ethyl ester added to the solution. One mol (109 g.) of dry ethyl bromide was then added over a period of thirty minutes and the whole refluxed for at least four hours. Most of the alcohol was evaporated and enough water added to just dissolve the sodium bromide formed. The oily layer was separated and distilled. The fraction boiling 190-196° was saved. Yields ranged from 70% to 80% of theory.

¹Behrend, Meyer, Buchholz, Ann., 314, 222 (1901).

²W. L. Terre, Master's Dissertation, University of Chicago, 1932.

³E. Lowe, Unpublished work.

O-ethyl urea was obtained by treating ethyl isourea hydrochloride with potassium hydroxide according to the process outlined by Terre.¹ Yields obtained were 85-90% of theory.

B. Removal of ethoxy group from 2-ethoxy-4-methyl-5-ethyl-6-oxypyrimidine.

2-Ethoxy-4-methyl-5-ethyl-6-oxypyrimidine (20 g.), mentioned above, were added to 1200 cc. of hot (85°) dilute (1:3) hydrochloric acid. There was an immediate evolution of ethyl-chloride² gas as the pyrimidine dissolved. After evaporating the solution to 150-200 cc. at 70° with a stream of air, the liquid was chilled in an ice and salt bath. The precipitated 4-methyl-5-ethyl-uracil was filtered off and recrystallized from hot water. A second crop was obtained by further concentration of the solution. The yield was 14.7 g. of the uracil, or 87% of theory. A melting point of 237-238° was observed.

11. Ethyl isourea hydrochloride, $\text{NH:C(OC}_2\text{H}_5\text{).NH}_3^+ \text{] Cl}^-$

A. Preparation of cyanamide from commercial calcium cyanamide.

Cyanamide was originally prepared by a reaction indicated by the equation:³



Basterfield⁴ developed the method of getting cyanamide in quantity from commercial calcium cyanamide. All materials involved are relatively inexpensive. The general method outlined by

¹W. L. Terre, loc. cit.

²W. L. Terre, loc. cit.

³Stieglitz and McKee, Am. Chem. J., 26, 209 (1901).

⁴S. Basterfield, Doctorate Dissertation, University of Chicago, 1920.

Basterfield,¹ with modifications by Terre² was used by the present author with some changes which increased the yields.

Commercial calcium cyanamide (4260 g.) was stirred with 15 liters of water by a mechanical stir for eighteen hours. There was no settling out of the solid by this procedure. The liquid was then filtered off by suction, made slightly acid with 50% sulfuric acid, and finally brought just on the alkaline side with powdered calcium carbonate. A heavy precipitate of calcium sulfate and excess calcium carbonate was removed by filtration and a concentrated solution of sodium carbonate added to the filtrate to precipitate a maximum of calcium carbonate. The mixture was again filtered and the filtrate made definitely acid with glacial acetic acid. The solution (approximately 10 liters) was divided into three parts and, since high temperatures tend to polymerize cyanamide, each was evaporated to dryness as speedily as possible at 40-70°. An apparatus was used by the author that proved to be quite effective in removing water from a substance. A three-liter round-bottomed flask was fitted with a bubbler and a glass connection of 12 to 14 mm. tubing that led to a condenser having a spiral inner tube. A good water pump was inserted into the system by connecting it to a large suction flask attached to the bottom of the condenser. By maintaining a pressure of 25 to 30 mm. with good bubbling in the flask, as much as 300-350 cc. of water was removed per hour when the bath was kept at 55-65°. When the volume of each portion of the solution was reduced about one half, it was chilled and filtered to get rid of a bulky inorganic precipitate. Approximately 12 hours of actual evaporation was required to get each part almost to dryness.

¹Ibid.

²W. L. Terre, loc. cit.

About 700 cc. of ether, dried over calcium chloride, was added to the residue from each part of the evaporation and the mixture shaken with 150 g. of anhydrous sodium carbonate to neutralize the excess acetic acid. The ether solution was then dried with about 600 g. of anhydrous sodium sulfate added in 50 g. portions with thorough shaking. The mixture was filtered with suction and the solid extracted three more times with the same quantity of dry ether.

After evaporation of the ether,¹ the oil remaining was chilled to -12° . This crude cyanamide was dried in a vacuum desiccator over concentrated sulfuric acid for 12 hours. Two 400 cc. portions of absolute ether were used to extract the cyanamide from any polymer in each of the three fractions. The solution was filtered and most (not all) of the ether removed from the filtrate. By chilling this liquid to -12° in an ice and salt bath, pure cyanamide separated and was collected on a filter with suction. After drying in a vacuum desiccator over concentrated sulfuric acid for one or two days, the cyanamide was ready for conversion into ethyl isourea hydrochloride. A yield of 371 g. of pure cyanamide was obtained from the 4260 g. of starting material, or 17% of theory. Basterfield² records yields of 8-38.5 g. of cyanamide from 200 g. of starting material, or 8-37% of theory. Using the unmodified method reported by Terre,³ research students obtained yields of 0-8% during the period, 1933-1936.

¹Do not let temperature get above $50-55^{\circ}$ because the oil is so thick by that time that superheating occurs which may cause the material to explode.

²S. Basterfield, loc. cit.

³W. L. Terre, loc. cit.

B. Formation of ethyl isourea hydrochloride from cyanamide.

It was formed by treating a solution of cyanamide in absolute ethyl alcohol with dry hydrogen chloride. The method recorded by Terre¹ was used and yields of 88% were obtained.

12. 4-Methyl-5-bromo-uracil, $\text{NHCONH.C(CH}_3\text{):CBr.CO}$

Powdered 4-methyl uracil² (4.5 g.) was suspended in 75 cc. of carbon disulfide and 7 g. (20% excess) bromine added with cooling and shaking. The mixture was then placed on a shaker for one day. The red solid was filtered off, dried in air for an hour, and finally warmed on a steam bath with good stirring to remove occluded bromine. The yield was 90-95% of theory. The compound decomposed at 235°, which agreed with the melting point listed by Wheeler and Merriam.³ The fact that bromine was in position 5 was ascertained by oxidation of brominated 4-methyl uracil with alkaline potassium permanganate and identification of the products formed. This confirmed the work done on the same compound by Offe.⁴

¹Ibid.

²Biltz and Heyn, Ann., 413, 108 (1917).

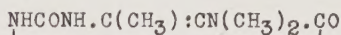
³Am. C. J., 29, 478 (1903).

⁴G. Offe, Ann., 353, 272 (1907).

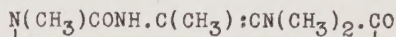
SUMMARY

1. The following uracils were prepared and their physical constants determined:

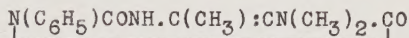
a. 4-Methyl-5-dimethylamino uracil,



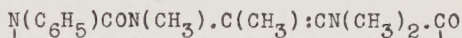
b. 1-4-Dimethyl-5-dimethylamino uracil,



c. 1-Phenyl-4-methyl-5-dimethylamino uracil,



d. 1-Phenyl-3-4-dimethyl-5-dimethylamino uracil,



2. A monobromo uracil was prepared from 4-methyl-5-ethyl uracil. The products obtained from oxidation of fresh and old brominated material indicated that the bromine atom entered position 5, but migrated on standing to the side chain on position 4.

3. Brominated 4-methyl-5-ethyl uracil was treated with ethyl magnesium bromide in an attempt to get a 5,5-diethyl uracil. The reaction was unsuccessful.

4. The preparation of cyanamide from commercial calcium cyanamide was reviewed, and modifications in the procedure presented to increase the yield.

In conclusion, the author wishes to express his appreciation to Professor Stieglitz for the guidance which has made this work possible; and to Dr. R. W. Johnson for his helpful suggestions.

